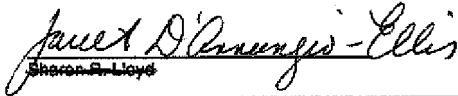


Docket No.: W0571.70010US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Thomas Tuschl et al.
Serial No.: 09/821,832
Confirmation No.: 6420
Filed: March 30, 2001
For: RNA SEQUENCE-SPECIFIC MEDIATORS OF RNA
INTERFERENCE
Examiner: Wollenberger, Louis V.
Art Unit: 1635

Certificate of Electronic Filing Under 37 CFR 1.8	
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with § 1.8(a)(4).	
Dated: <u>12/12/08</u>	 Sharon A. Lloyd

DECLARATION OF PHILLIP ZAMORE UNDER 37 C.F.R. §1.132

I, Phillip Zamore state and declare the following:

1. I am a co-inventor of the above-identified patent application with, David Bartel, Thomas Tuschl and Phillip Sharp.
2. I received my A.B. (1986) and Ph.D. (1992) from the Department of Biochemistry and Molecular Biology at Harvard University. I received a Life Sciences Research Foundation and a Charles H. Hood Fellowship to do postdoctoral work at the Whitehead Institute at the Massachusetts Institute of Technology. I joined the Department of Biochemistry and Molecular Biology at the University of Massachusetts Medical School as a faculty member in November 1999 and am a 2000 Pew Scholar in the Biomedical Sciences. In 2002, I became a W.M. Keck Foundation Young Scholar in Medical Research. I am presently the Gretchen Stone Cook Chair of Biomedical Sciences and a Howard Hughes Medical Institute (HMMI) investigator.

3. I receive financial compensation from certain licensees of the technology claimed in the instant patent application. I am also a co-founder and member of the Scientific Advisory Board of Alnylam Pharmaceuticals, one of licensees in the technology.

4. I have reviewed the above-identified patent application, the pending claims, the Office Action dated July 12, 2008, and the cited prior art references: Crooke et al. (US Patent 6,107,094), as evidenced by Tuschl et al. (US 20040259247 A1) and Amarzguioui et al. (2003) *Nucleic Acids Res.* 31:589-595.

5. The technology described in Crooke et al. relates to single stranded antisense "gapmer" oligonucleotides for use mediating double-stranded RNase (dsRNase)-mediated mRNA cleavage. The use of certain dsRNAs as artificial substrates for studying the mechanism of dsRNase-mediated mRNA cleavage is also described in the patent.

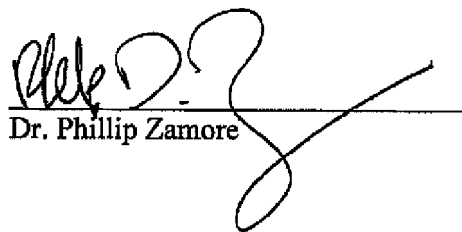
6. The instant invention is based on the discovery that dsRNA of about 21 to 23 nucleotides mediates RNA interference (RNAi). As described in the instant specification, the range of about 21 to 23 nucleotides is important for achieving RNAi. The discovery that isolated dsRNA of about 21 to 23 nucleotides could mediate RNAi was unexpected because, prior to the instant invention, it had been understood by those skilled in the art that longer segments of dsRNA were the mediators of RNAi. The discovery that an endogenous cellular process cleaves longer dsRNA into short dsRNA of the claimed size range, as described in the instant specification, led to the recognition that RNAi could be achieved by introducing smaller dsRNA into a cell or organism. Double-stranded RNA in this size range also eliminated the problem of interferon induction and cell death that occurred with longer double-stranded molecules. The results described in the specification were superior and unexpected for the entire claimed range of 21-23 nucleotides compared to the teachings of the prior art.

7. It was unexpected at the time of the invention that dsRNAs of the claimed length (21-23 nucleotides) would be highly efficient mediators of RNAi. This unexpected discovery formed the basis for the widespread application of RNAi in mammalian cells and organisms for a variety

of purposes. Thus, the selection of the claimed size range of 21-23 nucleotides was of critical importance.

8. Based on Crooke, at the time of filing of the pending application, it would have been unexpected and surprising that dsRNA of about 21 to 23 nucleotides would mediate RNAi.

I, the undersigned, declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this document and any patent which may issue from the above-identified patent application.


Dr. Phillip Zamore

12 December 2008
Date